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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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PARKIN, J	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/146,783	Applicant(s) Deacon et al.
	Examiner Jeffrey S. Parkin, Ph.D.	Art Unit 1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 06/25/01.

2a)☒ This action is **FINAL.** 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 49, 50, 66, 67, 85, & 120-136 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 49, 50, 66, 67, 85, & 120-136 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some* c)☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)

16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18)☐ Interview Summary (PTO-413) Paper No(s). _____

19)☐ Notice of Informal Patent Application (PTO-152)

20)☐ Other:

Response to Amendment

Status of the Claims

1. Acknowledgement is hereby made of receipt and entry of the amendment filed 25 June, 2001. Claims 1-48, 51-65, 68-84, and 86-119 were canceled without prejudice or disclaimer, claims 49, 50, 66, and 67 amended, and new claims 120-136 submitted. Claims 49, 50, 66, 67, 85, and 120-136 are pending in the instant application.

35 U.S.C. § 112, Second Paragraph

2. Claim 85 stands rejected under 35 U.S.C. § 112, second paragraph, as being vague and indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim continues to reference features from a non-elected group. Applicants are again reminded of the restriction requirement set forth *supra* and in the last Office action. As previously set forth, the claim should be amended to reflect the requirement and election (i.e., A vaccine composition comprising a non-pathogenic HIV-1 isolate ...).

35 U.S.C. § 112, First Paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. The previous rejection of claim 65 under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure for the claimed invention, is hereby withdrawn in response to applicants' amendment. It is also noted that the non-pathogenic HIV-1 isolates

having the designations V94101706, V941031169, and V95031022 have been deposited under the terms of the Budapest Treaty.

5. Claims 49, 50, 66, 67, and 85, as well as newly submitted claims 120-136, are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims have been amended to include additional limitations specifying that the HIV-1 isolate of interest has a deletion in the *nef*/LTR coding/regulatory region. Applicants argued that the claimed invention is fully enabled and provided a number of exhibits (B and C) in support of this contention. Applicants' arguments have been carefully considered, however, the rejection is still maintained for the reasons of record previously set forth in the last Office action and as further elaborated below.

Concerning the submission of Exhibit C, Applicants are reminded that in order to overcome a *prima facie* case for lack of enablement, applicants must demonstrate that the disclosure was enabled as of the filing of the application (see M.P.E.P. § 2164.05(a)). Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. *In re Gunn*, 537 F.wd 1123, 1128, 190 U.S.P.Q. 402, 405-06 (C.C.P.A. 1976). *In re Budnick*, 537 F.2d 535, 538, 190 U.S.P.Q. 422, 424 (C.C.P.A. 1976). Thus, this exhibit cannot be properly relied upon to demonstrate that the disclosure was enabled at the time of filing. Moreover, even if this exhibit was relied upon, it still fails to address a number of the defects previously noted by the Examiner.

As previously set forth, a number of concerns were raised in the

last Office action by the Examiner. Each of these will be addressed vis-a-vis applicants' response as follows:

1) It was previously argued by the Examiner that the specification fails to provide sufficient guidance pertaining to the selection of mutations, truncations, or decanucleotide deletions in the HIV-1 viral genome that will produce viruses of the desired non-pathogenic phenotype. Applicants' amendment and Exhibit B adequately address this concern.

2) As previously set forth, the prior art teaches that many viral and host factors contribute to the pathogenicity of any given isolate. Deciphering the molecular viral and cellular determinants contributing to this process has been quite problematic. Applicants' amendment and Exhibit B provide arguments and evidence suggesting that the SBBC patients were all infected with viruses that share common genotypic/phenotypic characteristics (e.g., a deletion in the *nef*/LTR region). However, these arguments and data do not exclude the possibility that host factors and other viral factors may also contribute to the LTNP state in these individuals.

3) As previously argued, it was asserted that the specification fails to disclose which components, parts, fragments, or derivatives thereof, contain the molecular determinants governing pathogenicity. Applicants' amendment and Exhibit B adequately address this concern.

4) The specification fails to provide adequate guidance concerning the selection of allelic variants of *nef*, or any other HIV viral gene, that contain the requisite phenotypic properties. This concern has not been addressed by applicants' response. The SBBC patients were all infected with the same parental virus. Thus, it is not readily manifest, given the teachings of Terwilliger *et al.* (1991), whether these findings can be extended to other HIV-1 isolates other than those described in the specification. As previously stated, it was observed in the literature that allelic

variants of *nef* provide different contributions to the replicative properties of HIV-1. Terwilliger *et al.* (1991) reported the following:

> The effects of the viral gene *nef* on human immunodeficiency virus type 1 (HIV-1) replication in culture were investigated using *nef* alleles of the HIV-1 IIIB and ELI strains. The results demonstrate significant allelic variation in the effect of *nef* on virus replication in both an established human $CD4^+$ T-cell line and primary human lymphocytes. In the context of HXB2 virus, the ELI *nef* allele but not the IIIB *nef* allele permits initiation of efficient low-multiplicity infection in primary peripheral blood mononuclear cells, including unfractionated peripheral blood lymphocytes, T cells, and monocyte/macrophages. **Within the same genetic context, the IIIB *nef* allele slightly retards replication of the virus in a T-cell line, whereas the ELI *nef* allele accelerates replication of the virus.** Sequences in the IIIB and ELI genomes outside of *nef* also moderate the effects of *nef* on HIV-1 replication.

In view of the teachings of the prior art, how could the skilled artisan reasonably predict which *nef* allelic variants will produce the desired LTNP phenotype?

5) It was previously argued that the specification fails to clearly set forth those criteria that the skilled artisan should employ to ascertain the pathogenic properties of any given variant. Applicants' amendment and Exhibit B adequately address this concern.

6) The specification fails to demonstrate that the instantly claimed HIV-1 vaccines or therapeutics employing *nef*⁻ deletion variants would mount an efficacious humoral or cellular immune response resulting in the prevention or treatment of HIV infection and the clinical sequelae leading to AIDS. A number of attendant caveats associated with the development of an efficacious HIV-1 vaccine or therapeutic were reviewed by Graham *et al.* (1995) and Haynes (1993). The rational design of an effective vaccine requires a knowledge of the pathogenesis of HIV infection and an

understanding of the human correlates of protective immunity. The cruxes associated with vaccine development can be summarized as follows:

a) The correlates of human protection remain to be elucidated. Thus, it is not clear if humoral, cell-mediated, or both types of immune response will provide protection.

b) The plasticity, or quasispecies nature, of the HIV-1 genome and its contribution to immune escape are salient factors that have prevented the development of effective HIV-1 vaccines and therapeutics. Convincing data demonstrating that such a vaccine can neutralize diverse field isolates remains to be presented.

c) The most appropriate methods for presenting viral antigens to the immune system remains to be elucidated. Thus, it is not readily manifest which mechanisms will optimize MHC Class I- or II-dependent antigen uptake, processing, compartmentalization, and presentation.

d) The viral antigens that confer protective immunity remain to be elucidated. Thus, the skilled artisan cannot predict which immunogens (i.e., Gag, Pol, Env) should be included in a putative vaccine and the form they should take (i.e., whole viral vaccine, sub-unit).

e) The viral and cellular determinants responsible for mucosal immunity remain to be elucidated. This route of administration plays a major role in viral transmission. Any efficacious vaccine will need to generate a strong mucosal immune response, probably through the production of neutralizing secretory IgA antibodies, to prevent the mucosal transmission of HIV-1.

f) Adequate animal models are not available for vaccine efficacy testing. Although animal models, such as the macaque system, are capable of providing important information pertaining to the understanding of pathogenesis and immunity, the results from such studies can not be directly extrapolated to a clinical

setting. Graham *et al.* (1995) specifically note (refer to pp. 1333-1334) that the **"structural differences between SIV and HIV complicate the direct translation to humans of the results of vaccine studies in the SIV-macaque system"** and that **"no animal model has been found in which an AIDS-like illness develops from a virus with the antigenic determinants of HIV-1."** It was further emphasized by Haynes (1993; refer to p. 1280) that **"In spite of an extraordinary amount of work in search of an animal model for human AIDS, no animal model exactly mirrors human HIV infection."**

These factors have not been adequately addressed by applicants' response and exhibits. Nothing in Exhibit B addresses these various caveats. Moreover, Exhibit C actually supports the Examiner's position. For instance, Dyer et al. (199) report (see Abstract, p. 436) that "Proposals for the use of live attenuated human immunodeficiency virus (HIV) type 1 (HIV-1) as a vaccine candidate in humans have been based on the production afforded by attenuated simian immunodeficiency virus in the macaque model ... **it is not yet known if this strategy could succeed in humans".** Applicants appear to be suggesting that HIV-1-specific CTL responses may confer protection against the invading pathogen. However, this study (see Abstract, p. 436) noted that "**Two of seven patients had weak CTL responses, and in one recipient, no HIV-specific CTLs were detected.**" Thus, nearly half of this sample population did not have strong HIV-1-specific CTL responses. This only illustrates the complexities associated with trying to ascertain which viral immunogens are capable of providing a protective or therapeutic immune response. Moreover, the failure to elicit strong CTL responses in these individuals may be due to the replication-impaired state of the virus. Thus, it is not readily manifest how a replication-impaired virus that replicates to such low levels would be capable of producing a robust immune

response that would lead to viral inactivation and clearance. The authors further report (see p. 441, rt. col., bridging paragraph) that "**our recent follow-up of these individuals suggests that slow disease progression may be occurring in some members with detectable viral replication. Also, declining CTLp levels in C98 suggest that CTLs may fail to adequately control viral replication in the future.**" The authors conclude (see p. 442, last paragraph) that "**We suggest that a potential vaccine candidate would require further attenuation than that in the natural SBBC viral strain ... whether such responses are capable of protecting against wild-type HIV-1 challenge remains to be determined.**" Clearly, there are a number of issues that remain to be resolved before any attenuated live HIV-1 vaccine can be utilized.

7) The prior art (Ruprecht *et al.*, 1995) raises a number of additional concerns pertaining to the development of an AIDS vaccine involving *nef*-deficient viruses. The findings of this article can be summarized as follows: a) SIV mutants containing *nef*, *vpr*, and negative regulatory element (NRE) deletions replicated to high levels following oral administration to infant macaques. All of the animals receiving this "vaccine" either developed SAIDS or display symptoms of the disease (Baba *et al.*, 1995). b) The *nef* gene product is not a direct molecular determinant for virulence. Nef appears to modulate the viral load while other determinants are responsible for the direct pathogenic properties of the virus. Accordingly, *nef*-deficient viruses are replication-impaired, not avirulent, and can be activated (thereby becoming virulent) by additional host, bacterial, or viral factors. c) Protective immune responses to SIV *nef* mutants developed quite slowly following administration of the putative vaccine. A dilatory immune response in humans could facilitate spread of the disease through high risk behavior by encouraging a false sense of protection. d) Replication-impaired retroviruses still undergo

integration into the host chromosome. This activity can potentially result in insertional mutagenesis. Disseminated lymphoproliferative disorders were associated with the administration of an SIV *nef* "vaccine". The authors soundly conclude (refer to page 178, final paragraph) that **"We feel that it is premature to consider *nef*-deleted viruses as candidate AIDS vaccines; they are neither safe nor sufficiently effective. The race between vaccine-virus replication and host defenses could be decided in favour of virus replication in coinfected or immunocompromised hosts."** These concerns were not adequately addressed by applicants' response or accompanying exhibits. Accordingly, when the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

New Grounds for Rejection

35 U.S.C. § 112, Second Paragraph

6. Newly submitted claims 122, 124, 129, and 134 are rejected under 35 U.S.C. § 112, second paragraph, as being vague and indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims include the limitation "about 10 nucleotides" which is ambiguous since the precise metes and bounds of the subject matter desired cannot be readily ascertained. For instance, do the claims encompass a deletion of 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 nucleotides? Appropriate amendment of the claim language is required.

Finality of Office Action

7. Applicants' amendment necessitated any and all new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy

as set forth in 37 C.F.R. § 1.136(a). **A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.**

Correspondence

8. Applicants are again reminded that the Art Unit location of this application in the Patent and Trademark Office has changed. To facilitate the correlation of related papers and documents for this application, all future correspondence should be directed to **art unit 1648.**

9. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242 or (703) 305-3014. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 308-4426. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

10. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from 8:30 AM to 6:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, James Housel or Laurie Scheiner, can be reached at (703) 308-4027 or (703) 308-1122, respectively. Any inquiry of a general nature or relating to the

status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

22 September, 2001

LAURIE SCHEINER
PRIMARY EXAMINER